Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (Currently amended) A method for treating hyperlipidemia in a mammal, said method comprises a step of administering to said mammal an effective amount of an RAR antagonist or an RAR inverse agonist ~~to treat hyperlipidemia caused other than by the administration of retinoids to the mammal~~ without coadministering a retinoid to said mammal.

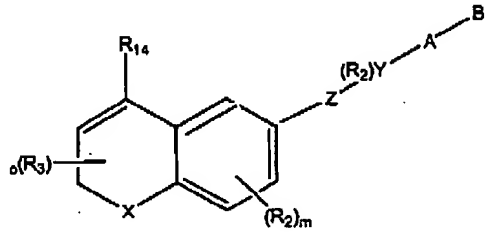
2. (Original) A method of claim 1 wherein said RAR is selected from the group consisting of RARα, RARβ, and RARγ.

3. (Original) A method of claim 1 wherein said RAR antagonist or an RAR inverse agonist is effective to lower the level of circulating lipid in a mammal, including a human being.

4. (Original) A method of claim 1 wherein said RAR antagonist or an RAR inverse agonist is effective to lower the level of circulating triglyceride in a mammal, including a human being.

5. (Previously presented) A method of claim 1 wherein said RAR antagonist or an RAR inverse agonist acts as a prophylaxis of myocardial infarction.

6. (Original) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



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wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $[C(R_1)_2]_n$ where R_1 is independently H or alkyl of 1 to 6 carbons, and n is an integer between, and including, 0 and 2, and;

R_2 is independently hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons, and;

R_3 is independently hydrogen, lower alkyl of 1 to 6 carbons or F, and;

m is an integer having the value of 0 - 3, and;

o is an integer having the value of 0 - 3, and;

Z is -C≡C-,

-N=N-,

$-N=CR_1-$,

$-CR_1=N$,

$-(CR_1=CR_1)_{n'}-$ where n' is an integer having the value 0 - 5,

$-CO-NR_1-$,

$-CS-NR_1-$,

$-NR_1-CO$,

$-NR_1-CS$,

-COO-,

-OCO-;

-CSO-;

-OCS-;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups, or

when Z is $-(CR_1=CR_1)_{n'}-$ and n' is 3, 4 or 5 then Y represents a direct valence bond between said $(CR_2=CR_2)_{n'}$ group and B;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

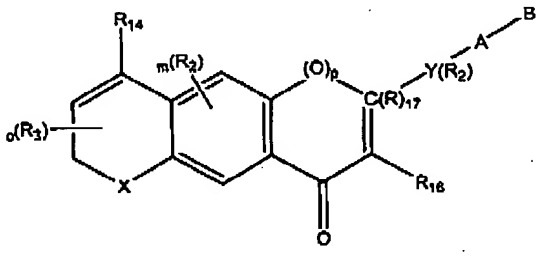
B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, and

R_{14} is $(R_{15})_r$-phenyl, $(R_{15})_r$-naphthyl, or $(R_{15})_r$- heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5, and

R_{15} is independently H, F, Cl, Br, I, NO_2, $N(R_8)_2$, $N(R_8)COR_8$, $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an

alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons.

7. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $[C(R_1)_2]_n$ where R_1 is independently H or alkyl of 1 to 6 carbons, and n is an integer between, and including, 0 and 2, and;

R_2 is independently hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons, and;

R_3 is independently hydrogen, lower alkyl of 1 to 6 carbons or F, and;

m is an integer having the value of 0, 1, 2, or 3, and;

o is an integer having the value of 0, 1, 2, or 3, and;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups, and;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds, and;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, and;

R_{14} is $(R_{15})_r$-phenyl, $(R_{15})_r$-naphthyl, or $(R_{15})_r$- heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0,1, 2, 3, 4 or 5, and;

R_{15} is independently H, F, Cl, Br, I, NO_2, $N(R_8)_2$, $N(R_8)COR_8$, $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons, and;

R_{16} is H, lower alkyl of 1 to 6 carbons, and;

R_{17} is H, lower alkyl of 1 to 6 carbons, OH or $OCOR_{11}$, and;

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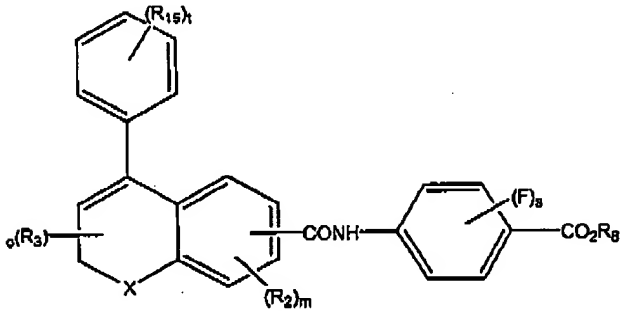
p is zero or 1, with the proviso that when p is 1 then there is no R_{17} substituent group, and m is an integer between, and including, 0 and 2.

8. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



where X is $C(R_1)_2$ or O, and;

R_1 is H or alkyl of 1 to 6 carbons, and;

R_2 is independently lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons, and;

m is an integer having the value of 0-3, and;

R_3 is independently lower alkyl of 1 to 6 carbons or F, and;

o is an integer having the value of 0-3, and;

s is an integer having the value of 1-3, and;

R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, and;

R_{15} is independently H, F, Cl, Br, I, NO_2, $N(R_8)_2$, COR_8, $NR_8CON(R_8)_2$, $OCOR_8$, OR_8, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds,

an alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons, and;

t is an integer having the values of 0, 1, 2, 3, 4, or 5, and;

the CONH group is in the 6 or 7 position of the benzopyran, and in the 2 or 3 position of the dihydronaphthaline ring, or a pharmaceutically acceptable salt of said compound.

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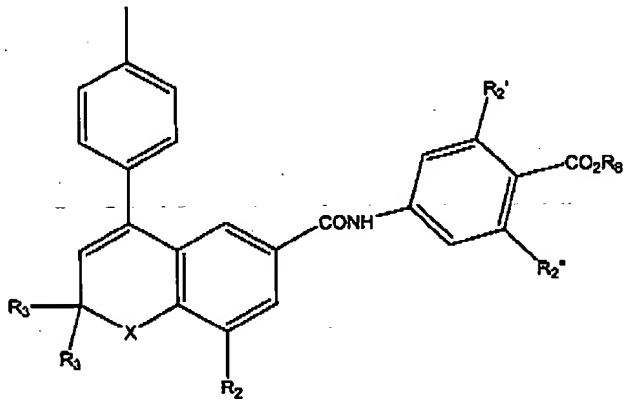
9. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



where X is $C(CH_3)_2$ or O, and;

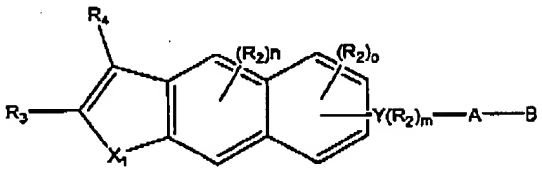
R_2 is H or Br, and;

$R_{2'}$ and $R_{2''}$ independently are H or F, and;

R_3 is H or CH_3, and;

R_8 is H, lower alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

10. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



wherein X_1 is: $-C(R_1)_2-$, $-C(R_1)_2-C(R_1)_2-$, $-S-$, $-O-$, $-NR_1-$, $-C(R_1)_2-O-$, $-C(R_1)_2-S-$, or $C(R_1)_2-NR_1-$; and

R_1 is independently H or alkyl of 1 to 6 carbons; and

R_2 is optional and is independently defined as lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, fluoro substituted alkyl of 1 to 6 carbons, OH SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons; and

m is an integer between, and including, 0 and 4; and

n is an integer between, and including, 0 and 2; and

o is an integer between, and including, 0 and 3; and

R3 is H, lower alkyl of 1 to 6 carbons, F, Cl, Br or I; and

R4 is $(R_5)_p$-phenyl, $(R_5)_p$-naphthyl, $(R_5)_p$-heteroaryl where the heteroaryl group is five-membered or 6-membered and has 1 to 3 heteroatoms selected from the group consisting of O, S, and N; and

p is an integer between, and including, 0 and 5; and

R_5 is optional and is defined as independently F, Cl, Br, I, NO_2, $N(R_8)_2$, $N(R_8)COR_8$, $N(R_8)CON(R_8)_2$, OH, $OCOR_8$, OR_8, CN, COOH, $COOR_8$, an alkyl group having from 1 to 10 carbons, an alkenyl group having from 1 to 10 carbons and 1 to three double bonds, alkynyl group having from 1 to 10 carbons and 1 to 3 triple bonds, or a (trialkyl)silyl or (trialkyl)silyloxy group where the alkyl groups independently have from 1 to 6 carbons; and

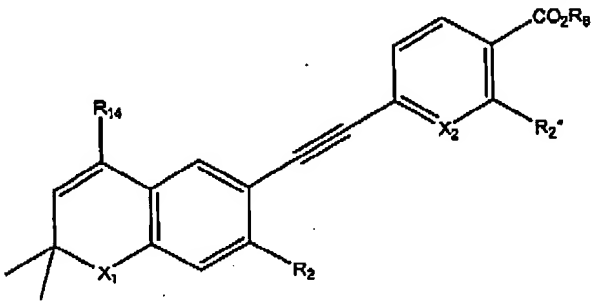
Y is a phenyl or naphthyl group, or a heteroaryl selected from the group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups, or Y is $-(CR_3=CR_3)_r-$; and

r is an integer between, and including, 1 and 3; and

A is $(CH_2)_q$ where q is an integer from 0-5, lower branched chain alkyl having from 3 to 6 carbons, cycloalkyl having from 3 to 6 carbons, alkenyl having from 2 to 6 carbons and 1 or 2 double bonds, alkenyl having from 2 to 6 carbons and 1 or 2 triple bonds, with the proviso that when Y is $-(CR_3=CR_3)_r-$ then A is $(CH_2)_q$ and q is 0; and

B is H, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or $Si(C_{1-6}alkyl)_3$, wherein R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl, where the alkyl groups has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are H, a lower alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is a divalent alkyl radical of 2-5 carbons.

11. (Original) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



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where X_1 is S or O;

X_2 is CH or N;

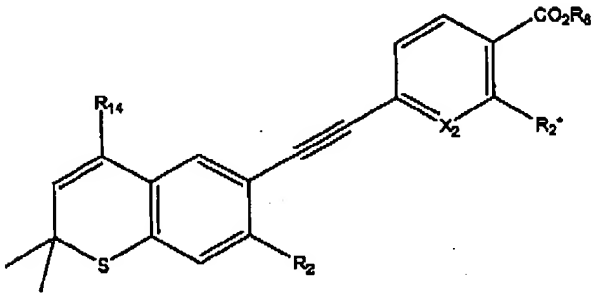
R_2 is H, F, CF_3 or alkoxy of 1 to 6 carbons;

R_2* is H, F, or CF_3;

R_8 is H, or lower alkyl of 1 to 6 carbons;

R_{14} is unsubstituted phenyl, thienyl or pyridyl, or phenyl, thienyl or pyridyl substituted with one to three R_{15} groups, where R_{15} is lower alkyl of 1 to 6 carbons, chlorine, CF_3, or alkoxy of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

12. (Original) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



wherein X_2 is CH or N, and;

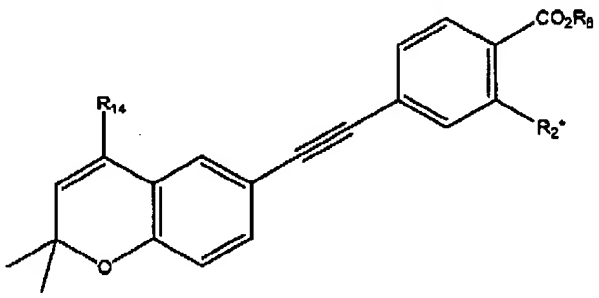
R_2 is H, F, or OCH_3, and;

R_2* is H or F, and;

R_8 is H, or lower alkyl of 1 to 6 carbons, and;

R_{14} is selected from the group consisting of phenyl, 4-(lower-alkyl)phenyl, 5-(lower alkyl)-2-thienyl, and 6-(lower alkyl)-3-pyridyl where lower alkyl has 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

13. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:

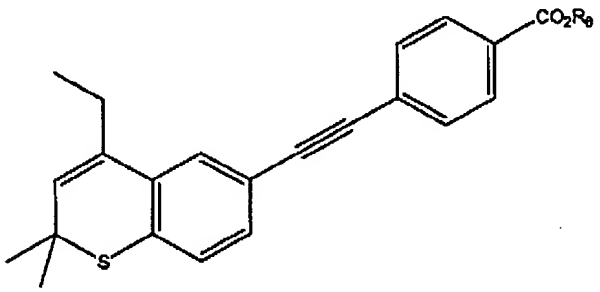


where R_2* is H or F;

R_8 is H, or lower alkyl of 1 to 6 carbons, and

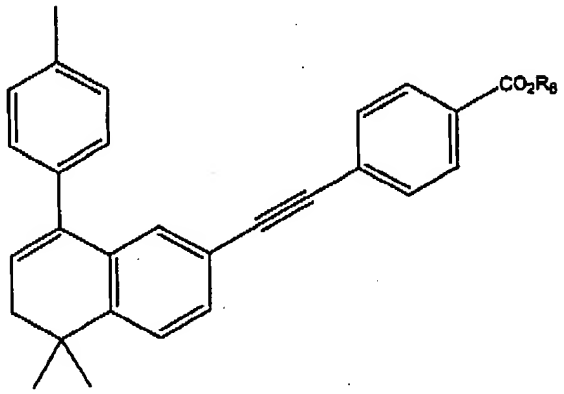
R_{14} is selected from the group consisting of phenyl, and 4-(lower-alkyl)phenyl, where lower alkyl has 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

14. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



where R_8 is H, lower alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

15. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



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where R_8 is H, lower alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

16. (Original) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:

$Y_3(R_4)-X-Y_1(R_1R_2)-Z-Y_2(R_2)-A-B$

Where Y_1 is phenyl, naphthyl, or heteroaryl selected from the group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazonyl, ozazolyl, imidazolyl, and pyrrazolyl, said phenyl, naphthyl, and heteroaryl groups being substituted with an R_1 group, and further substituted or unsubstituted with one or two R_2 groups;

R_1 is C_{1-10} alkyl, 1-ademantyl, 2-tetrahydropyranoxy, trialkylsilanyloxy where alkyl has up to 6 carbons, OH, alkoxy where the alkyl group has up to 10 carbons, alkylthio where the alkyl group has up to 10 carbons, or OCH_2OC_{1-6} alkyl;

R_2 is lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, CF_2CF_3, OH, OR_3, NO_2, $N(R_3)_2$, CN, N_3, COR_3, $NHCOR_3$, COOH, or $COOR_3$;

X is $(C(R_3)_2$, S, SO, SO_2, O or NR_3;

Z is -C≡C-,

-N=N-,

$-N(O)=N-$,

$-N=N(O)-$,

$-N=CR_3-$,

$-CR_3=N$,

$-(CR_3=CR_3)_n-$ where n is an integer having the value 0 - 5,

$-CO-NR_3-$,

$-CS-NR_3-$,

$-NR_3-CO$,

$-NR_3-CS$,

$-COO-$,

$-OCO-$;

$-CSO-$;

$-OCS-$; or

$-CO-CR_3=R_3-O$,

R_3 is independently H or lower alkyl of 1 to 6 carbons;

Y_2 is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with one or two R_2 groups, or

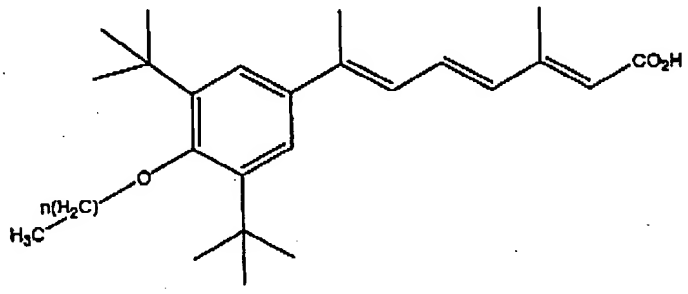
when Z is $-(CR_3=CR_3)_n-$ and n is 3, 4 or 5 then Y_2 represents a direct valence bond between said $-(CR_3=CR_3)_n$ group and B;

Y_3 is phenyl, naphthyl, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with one to three R_4 groups, where R_4 is alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 triple bonds, F, Cl, Br, I, NO_2, CN, NR_3, N_3, COOH, $COOC_{1-6}$ alkyl, OH, SH, OC_{1-6} alkyl, and SC_{1-6} alkyl;

A is $(CH_2)_q$ where q is from 0-5, lower branched alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl, having 2-6 carbons and 1-2 double bonds, alkynyl having 2-6 carbons and 1 to 2 triple bonds, and

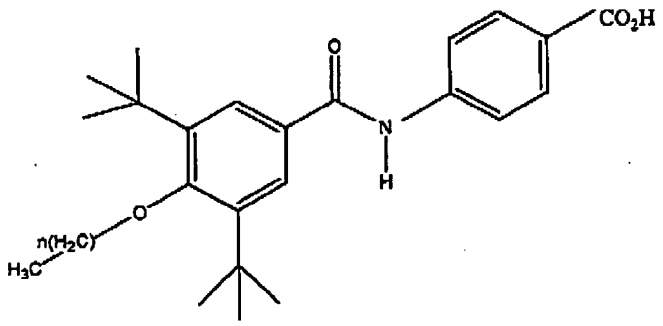
B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or $Si(C_{1-6}$ alkyl$)_3$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

17. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



where n is an integer from 1 to 10.

18. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



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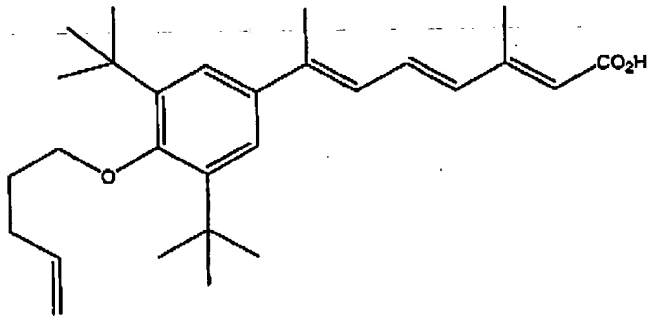
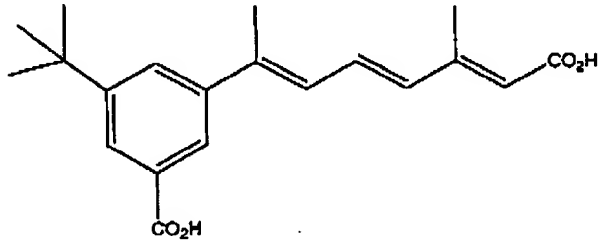
where n is an integer from 1 to 10.

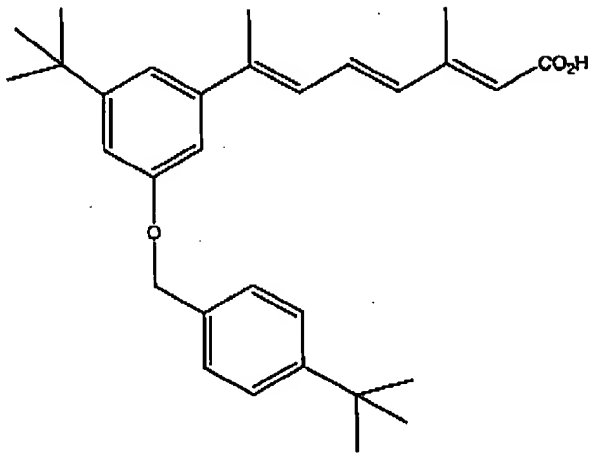
19. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



20. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



21. (Withdrawn) A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



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22. (Original) A method of claim 1 wherein the RAR antagonist or an RAR inverse agonist is administered orally.

23. (Original) A method of claim 1 wherein the RAR antagonist or an RAR inverse agonist is administered topically.

24. (Original) A method of claim 1 wherein the RAR antagonist or an RAR inverse agonist is administered systemically.

25. (Currently amended) A method for treating hyperlipidemia in a mammal, said method comprises a step of administering to said mammal an effective amount of 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid ~~to treat hyperlipidemia caused other than by the~~

~~administration of retinoids to the mammal~~ without coadministering a retinoid to said mammal.

C/Cont

26. (Previously presented) A method of claim 24 wherein the step of administering 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid lowers the level of circulating triglycerides.